BOX AF
EXPEDITED PROCEDURE
EXAMINING GROUP 1642
PATENT
599-158P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: Nobutaka IDA et al.

Appl. No.: 08/809,621 Group: 1642

Filed: June 2, 1997 Examiner: L. Sun Hoffman

For: DRUG FOR TREATING BONE DISORDERS

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

I, Teruo Matsushita-Nakadate, do hereby declare the following.

I am a citizen of Japan, residing at Imajuku 1-13-17, Asahi-ku, Yokohama-shi, Kanagawa 241-0817, Japan.

I am by profession a pharmacologist and have graduated from Tohoku University, Faculty of Science, Department of Chemistry in March 1973; in March 1975, I was conferred a Master's degree from the Department of Biochemistry and Chemistry of Tohoku University. In April 1975, I was

employed by the government of Japan and joined National Institute of Forensic Sciences. In April 1977, I was employed by the Department of Pharmacology, School of Medicine, Keio University as a research associate. In March 1983, I obtained a Ph.D. degree (doctor of medical science). From April 1985 to March 1987, I stayed as a visiting fellow in Molecular Mechanism of Tumor Promotion Section, Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, National Institute of Health, U.S.A. In April 1987, I became an Associate Professor of Keio University, School of Medicine. In April 1989, I was employed by Toray Industries, Inc. and joined Toray Basic Research Laboratories, Pharmacology Laboratory, as a section chief. In October 1995, I became the director of Pharmacology Laboratory of Toray Basic Research Laboratories.

From April 1989, I have been a part-time lecturer of Keio University, School of Medicine. I won the Encouragement Award of the Japanese Pharmacological Society in March 1988. My research fields have been neuropharmacology, circulation research, inflammation and bone metabolism. I have published more than 70 original papers in international journals.

I have carefully read the above-identified application, have read and understand the subject matter of the Office Actions of December 9, 1998, June 10, 1998 and September 24, 1997. In my opinion, the Examiner's allegations are incorrect. Specifically, regarding the rejection over Modi US 5,417,982, the passage of Modi cited by the Examiner is an erroneous description and/or wishful thinking by Modi, and further, the disclosed information is insufficient to allow a person skilled in the art to corroborate the alleged effect.

1. The contents of the passage of Modi cited by the Examiner is based on a misconception-

The Examiner relies on the underscored portion of the following citation of Modi Reference:

"The present invention may be used to entrap other growth hormones in a polymer matrix, e.g., estrogens, androgens, insulin, IGF, interleukin-I and interlleukin-II. Cytokines such as interferon-β and interferon-γ, used in the treatment of diseases such as osteoporosis, diabetes mellinus and multiple solerusis may also benefit from the present invention."

The description of the underscored portion of the passage is not correct. At the time of filing the application for Modi patent and before, IFN-β had not been

used as a therapeutic drug for osteoporosis patients. In addition, no report was available indicating the effectiveness of IFN-β in an osteoporosis model.

For caution's sake, a literature search was carried out to confirm this fact. The result supported my judgement as is shown in the attached chronological table. To the best of my knowledge, at the time Modi filed the application which issued as US 5,417,982, no literature was available teaching the use of IFN-β for the therapeutic treatment of osteoporosis. The description in the passage in question is not therefore correct.

2. Difficulty in confirming the effect of IFN-β for the therapeutic treatment of osteoporosis due to the lack of disclosure of a test method.

Assuming *arguendo* that the description in the relevant passage of Modi Reference (cited by the Examiner) is correct, Modi fails to give information about the manner of IFN-β administration and dose thereof. The only reference to IFN-β, apart from the passage in question, can be found in column 2, lines 36 to 37 and that in column 3, lines 56 to 57, wherein Modi only indicates that "these cytokines are

interferon-β and interferon-γ" and fails to provide information about usage or dosage.

It is not persuasive that Modi does not disclose his experimental information he retains. This logical conclusion is supported by the following background as well. As is clear from the attached chronological table, even for examples of IFN-α having no direct relationship with the present case, Miki et al teach that administration to hepatitis C patients (not osteoporosis patients) caused an increase in bone volume (Miki et al., J. Bone Min. Met., *11*, 39, **1993**), while Yamamoto et al report that no increase in bone volume was caused (Yamamoto et al., The 29th West District Conference of Japanese Association of Hepatology, **1994**, Abstract No. 187). That is, the effect of even the α-type is not clear, and the difference in result may be considered to reflect differences in therapeutic conditions. It would at least be necessary to disclose conditions of administration in order to prove validity of the result.

The only report referring to an increase or decrease in bone volume caused by IFN-β is that of Nilson et al. (Nilson et al., J. Interferon Res., 4, 135, 1984). And yet, even this report, only covers the case where murine IFN

comprising an α-β mixture was administered, and most importantly, the administration exerted no effect on the bone volume.

At the time of filing the application for the Modi Patent US 5,417,982, there was no information available about the effect of IFN-β on osteoporosis. This includes not only validity data but also more basic information.

The essence of the teachings of Modi lies in a novel carrier capable of containing physiologically active substances, permitting administration in vivo with the associated economic benefit. The novel carrier is taught to further improve the therapeutic effect of known useful physiologically active substances. This is clearly mentioned by Modi, under the heading of Background Art (column 1, lines 22 to 27).

As described above, Modi fails to teach the information required to treat osteoporosis with IFN-β, such as dosages, period of administration and route of administration. Therefore, in my opinion, it would require inventive skill to use IFN-β to treat osteoporosis based upon the limited disclosure of Modi, when taken in conjunction with the relevant art available at the instant priority date and the

skill of the ordinary artisan. It would be necessary for the artisan to conceive the idea that IFN-β has a therapeutic effect on osteoporosis and then perform experiments to find the appropriate treatment regimen (dosage, route of administration, period of administration and method for evaluating actual effect).

3. Description in the portion in question of Modi Reference is only a wishful thinking or an estimation -

In the above-cited passage, Modi makes similar allegations regarding the treatment of osteoporosis with IFN-γ. As in the case with IFN-β, this is not correct. Experimental results strongly suggesting a contrary conclusion for IFN-γ have been reported one year prior to filing of the application for the Modi Patent.

Using an animal model (Pediatrics Res., *33*, 384, **1994**) IFN-γ was found to be effective for the therapy of osteopetrosis. A similar therapeutic effect was thereafter confirmed for administration of human IFN-γ to human osteopetrosis patients (New Engl. J. Med., *332*, 1544, **1995**). While osteoporosis is a disease causing a decrease in bone volume, osteopetrosis causes an abnormal increase in bone

volume. More specifically, IFN-γ has a function of reinstating or improving osteopetrosis by reducing bone volume. Based upon these reports, the skilled artisan would reasonably conclude that when IFN-γ is administered to an osteoporosis patient already suffering from a decrease in bone volume, there would be a further acceleration in the decrease in bone volume which would lead to an increased state of osteoporosis.

If a researcher alleges that the bone volume can be increased with IFN-γ subject to conditions of administration, it is natural for the researcher to disclose such conditions in detail. Modi fails to disclose information regarding the conditions for administration. Based upon these facts, as one skilled in the art, I reasonably conclude that the passage in question of the Modi Reference can be considered wishful thinking or an estimation not based on a fact.

4. Modi does not limit wishful thinking to the treatment of osteoporosis -

I must frankly confess receiving a very strange impression as a result of careful reading of Modi. Modi

mentions that "IFN-γ [is] used in the treatment of diseases such as osteoporosis, diabetes mellitus and multiple sclerosis."

The lack of factual support for the Modi's allegation that IFN-β or IFN-γ is useful for the therapy of osteoporosis has already been described above. For diabetes mellitus also, IFN-β or IFN-γ have never been used as a therapeutic drug. Thus, Modi gives a false impression in this respect also.

If the essence of Modi Patent is to improve the pharmacological effect of existing useful substances or to achieve a higher efficiency of existing therapeutic methods, why didn't he cite cases of patients suffering from viral diseases for which a huge industrial usefulness of IFN-β and IFN-γ as therapeutic drugs had already been established (e.g., E.D. Maeyer and H. Schllekens (eds) in The Biology of the Interferon System 1983, Elsevier Science Publisher, 1983; Y. Kawade and S. Kobayashi (eds) in The Biology of the Interferon System, 1988, Kodansha Scientific Ltd., Tokyo, 1988; and S. Baron et al. (eds) in Interferon, Principles and Medical Applications, The University of Texas Medical Branch at Galveston, TX, 1922)? A literal reading of the

portion in question reveals the serious lack of reasonability and gives a strange impression.

In conclusion, Modi has made an improper description in above-cited passage. This passage is preceded by the following statement, "The present invention may be used to entrap other growth hormones in a polymer matrix, e.g., estrogens, androgens, insulin, IGF, interleukin-I and interleukin-II." From among the substances enumerated here, estrogen and IGF are effective for the treatment of osteoporosis, and insulin is a therapeutic drug of diabetes, all being in the public domain. In other words, a person skilled in the art could confirm these allegations by Modi, since the art has recognized a nexus between the compounds and their pharmaceutical effectiveness for the treatment of these diseases. Administration routes and effective dosages of these individual substances have been established, and although Modi does not provide sufficient information regarding administration routes and effective dosages of these individual substances within the four corners of the Modi patent, the artisan could find the necessary information from the art. Thus, making it possible to ratify the allegation of usefulness of these pharmaceutical

compounds by Modi.

According to a literal interpretation of the above-cited passage, the allegation by Modi regarding the treatment of osteoporosis with IFN-β or IFN-γ is fundamentally not true, and it is **not** within the skill of the artisan to confirm the usefulness of the IFN-β or IFN-γ as a therapeutic drug for the treatment of osteoporosis. Thus, Modi does not make the presently claimed invention obvious.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Teruo Matsushita Nakadate
Signature

2000. 6. 29
Date